Advancing the Calcium–Colorectal Cancer Hypothesis

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Two decades ago, Newmark et al. *(1)* implicated calcium intake in colorectal carcinogenesis. They hypothesized that calcium ions in the lumen of the large bowel neutralize the toxic effects of free ionized fatty acids and bile acids through the formation of insoluble mineral–fat complexes or soaps. Subsequent experiments *(2)* showed that calcium could inhibit colon cancer in animals. A particularly influential study *(3)* demonstrated that calcium supplementation reduced rectal epithelial cell proliferation in humans. Recent studies suggest that luminal calcium directly affects colorectal tumors via the calcium sensing receptor (CASR), which is located in the plasma membrane where it detects extracellular calcium concentration *(4);* investigation of CASR allelic variants may further clarify the role of calcium in colorectal carcinogenesis *(5).*

The epidemiology of calcium intake and colorectal cancer has evolved over time. Reviews of observational epidemiologic studies published through the mid- to late-1990s suggested little or no protective association between calcium intake and colorectal adenoma and cancer *(6).* Subsequently, a fairly consistent modest inverse association (risk reductions in the range of 15%–40% for the highest versus the lowest intake categories) has emerged from several prospective cohort studies *(7–9)* as well as large case–control studies with some 2000 colon cancer cases *(10).* Less consistency attends the dose–response relation, with some studies *(8)* showing no risk reduction beyond 700–800 mg of total calcium intake and others *(9–10)* demonstrating an inverse trend over the entire intake range.

Complementing this emerging consistency of an inverse calcium–colorectal cancer association are results from three polyp trials. In each of these, adenoma recurrence was lower in the calcium intervention arm compared with the control arm. The adenoma recurrence reduction (but not adenoma growth) was statistically significant in the first small trial, but a separate calcium effect could not be discerned because the intervention combined calcium and antioxidative vitamins *(11).* The 34% recurrence reduction in the European Cancer Prevention trial *(12)* did not attain statistical significance. In the Calcium Polyp Prevention Study (CPPS), in which the intervention was 1200 mg of elemental calcium daily, a 19% reduction in adenoma recurrence did reach statistical significance after only 1 year of intervention *(13).* The magnitude of adenoma recurrence reduction in this trial is in line with the size of the inverse associations seen in observational epidemiologic studies.

The original CPPS report described the effect of calcium supplementation on adenomas as a whole, with similar reductions in recurrence for small and large neoplasms. In this issue of the Journal, Wallace et al. *(14)* report that the risk of recurrence in the CPPS was lower for "advanced histology neoplasms" compared with that for tubular adenomas. In addition, they found some evidence that the calcium supplementation effect on adenoma recurrence was stronger among those with higher dietary intakes of calcium and fiber and lower consumption of fat.

Although the current report suggests refining of both the nutritional context and histopathologic target of calcium intervention, some caution is in order. The point estimate for adenoma recurrence was lowest for advanced as opposed to other types of colorectal neoplasms, but the recurrence reductions for the different histopathologic types were not statistically significantly different from one another. Clearly, the original study was not powered to determine histopathology-specific effects. Recognizing that, we might conclude that the observed differences highlight true and important biologic facts warranting further research. Alternatively, we might determine that there really are no histopathology-specific differences in this trial, the small observed point estimate differences merely reflecting chance variation.

A similar argument can be made with respect to potential interactions between calcium supplementation and dietary factors. Again, the trial was underpowered to detect such interactions. In that context, we could say there might be some noteworthy interactions, but we could comfortably conclude that the data are essentially null with respect to dietary modification of the calcium–neoplasia connection. [The original publication reported "no evidence" of effect modification by dietary calcium *(13).*]

Where are we, then, with respect to population-level evidence for the calcium–colorectal cancer hypothesis? We have increasingly consistent observational epidemiologic evidence from studies with colorectal cancer end points. We cannot, though, definitively rule out confounding as an explanation for the modest inverse associations seen in these observational epidemiologic studies. One trial demonstrates that calcium supplementation results in a statistically significant reduction in adenoma recurrence *(13).* The great strength of this trial is the randomized design that renders the intervention and control arms similar for both known and unknown confounders. It is, however, only one trial. Another adequately powered trial with similar results would be reassuring. In that vein, a new intervention study with the statistical power to detect a modest adenoma recurrence reduction for calcium is now underway (Baron JA: personal communication).

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There is an additional caveat for polyp trials: inferences from adenoma recurrence trials to invasive colorectal cancer can be problematic. It is at least theoretically plausible that an intervention (such as calcium) that reduces overall adenoma recurrence fails to reduce the recurrence of the small proportion of lesions that will progress to invasive carcinoma *(16)*. The interpretation of polyp data has been complicated even more by new research on the serrated neoplasia pathway *(17)*. Some lesions formerly classified as hyperplastic (and, in polyp trials, not considered as recurrent adenomas) are now classified as serrated adenomas, i.e., true neoplasms with dysplastic features.

Suppose the epidemiology remains consistent (some large cohort studies have yet to weigh in on the calcium versus colorectal cancer issue), the new calcium–adenoma recurrence trial is positive, and the Women's Health Initiative combined calcium–vitamin D component *(18)* shows a statistically significant reduction in colorectal cancer. The totality of this human population-level evidence would support a causal relation between calcium intake and colorectal cancer. Causality would not be guaranteed, however. We would still face the possibility of confounding in the observational data, uncertainties in making inferences from adenoma recurrence to invasive cancer, and the inability of the Women's Health Initiative to determine whether calcium plays an etiologic role independent of vitamin D. Nevertheless, the evidence, in sum, would be very strong.

We will not address here the public health implications of such a conclusion. There will be important questions to answer regarding not only dose but also form of intake. Can sufficient calcium be ingested via food? Or is supplementation necessary? We will want to figure into the public health equation possible noncancer benefits of increased calcium [fracture protection, for example *(19)*], as well as potential (but hardly established) adverse effects *(20,21)*. Moreover, a combination of calcium and vitamin D may turn out to be the preferred prevention regimen.

With respect to the original biologic hypothesis, studies are now in place with the potential to provide a compelling—almost proven—case that a nutritional factor (calcium) can alter the occurrence of malignant disease (colorectal cancer). That would be a tremendous advance.

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